PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 200M213-WO0	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/014887	International filing date *(day/month/year)* 12 May 2004 (12.05.2004)	Priority date *(day/month/year)* 12 May 2003 (12.05.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A61K 47/48, 38/00		
Applicant AFFYMAX, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 18 November 2005 (18.11.2005)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/014887	International filing date *(day/month/year)* 12.05.2004
Priority date *(day/month/year)* 12.05.2003	
International Patent Classification (IPC) or both national classification and IPC A61K47/48, A61K38/00	
Applicant AFFYMAX, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/014887

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-36 (partly)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☒ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☒	has not been furnished
	☐	does not comply with the standard
the computer readable form	☒	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 6, 8, 19, 21, 23, 34 and 36
	No:	Claims	1-3, 5, 7, 9-18, 20, 22, 24-33 and 35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1,2,5-17, 20-36
	No:	Claims	

2. Citations and explanations

   see separate sheet

III No opinion.

The applicant did not furnish a sequence listing. It follows that the international search report **was restricted** to subject matter for which no sequence listing was required (PCT Rule 13, PCT Rule 5.2 and Article 17(2)(a)PCT).
Consequently, no **positive** opinion will be formulated with respect to claims directed to this subject matter (Art. 34(4)(a)(I) PCT).

IV Lack of unity of invention.

The simplest form of a spacer of the formula depicted in claims 1 and 16, is a spacer of the formula -NH-C(O)-.Peptide-PEG conjugates comprising an -NH-C(O)- spacer, are obviously not novel, and should not need to be commented on (cf. for instance D1: US4179337).

The next simplest form of the spacer is that defined in claim 2, wherein both gamma and delta are equal to 0, resulting in a spacer of the formula -NH-(CH2)a--(CH2)e--Y (eg. invention 1).
This also represents **the linking concept** between the spacers as defined in inventions 1 and 2 below. The simplest form of the spacer of invention 1 is the amino acid beta-alanine (cf. claims 31 and 32).

Peptide-PEG conjugates comprising a beta-Ala linker are known in the art, cf. D2: WO-00/33881 (examples 15 and 16) and D3: WO-92/16555 (examples 2-8).

It thus follows that the subject matter of the present application must be divided into the following two separate inventions.

A: A conjugate comprising a peptide, a spacer and a water soluble polymer, wherein the spacer moiety is of formula: -NH-(CH2)n-Y. (hence, both .gamma. and .delta. are equal to o).
(Claims: 1, 2, 5-17, 20-30, 33-36 (all partial), and 31 and 32 (complete)).

B: A conjugate comprising a peptide, a spacer and a water soluble polymer, wherein the spacer moiety is of the formula: $-NH-(CH_2)_\alpha-[O-(CH_2)_\beta]_\gamma-O_\delta-(CH_2)_\varepsilon-Y$, wherein at least one of .gamma. or .delta. is larger then, or equal to, 1.
(Claims: 1, 2, 5-17, 20-30, 33-36 (all partial), and 3, 4 and 18, 19 (complete)).

V Reasoned Statement.

Subject matter of the present application.

The subject matter of the present application is the provision of conjugates, and pharmaceutical compositions thereof, comprising a peptide, a spacer and a water soluble polymer, wherein the conjugate is characterised by a spacer with the formula $-NH-(CH_2)_\alpha-[O-(CH_2)_\beta]_\gamma-O_\delta-(CH_2)_\varepsilon-Y$.

It is noted that the present application is one of a set of 4 applications from AFFYMAX, Inc., all dealing with overlapping subject matter (cf. US-04/14886-9, D17-D19).

Cited prior art documents (Rule 64(1) PCT).

D1: US-A-4 179 337.
D2: WO 00/33881 A.
D3: WO 92/16555 A.
D4: WO 00/24770 A.
D5: WO 98/25965 A.
D6: WO 96/40772 A.
D7: WO 96/40750 A.
D8: WRIGHTON ET AL. (1997) NATURE BIOTECHNOL. 15, 261-1265.
D9: GREENWALD ET AL. (Feb. 2003) ADV. DRUG DEL. REV. 55, 217-250.
D10: GREENWALD ET AL. (Apr. 2003) BIOCON. CHEM. 14, 395-403.
D11: US 2002/015691 A1.
D12: WO 96/40189 A.
D13: WO 00/24782 A.
D14: US 6113906 A.
D15: WO 02/065988 A.
D16: WO 2004/014424 A.
D17: WO 2004/101600 A.
D18: WO 2004/101606 A.
D19: WO 2004/101611 A.
D20: WO 2004/108070 A.

D16-D20 do not form part of the prior art under Rule 64(1) PCT.

Novelty (Art. 33(2) PCT).

D1 discloses the PEGylation of proteins and enzymes to render said proteins and enzymes non-immunogenic. D1 is cited as one of many examples disclosing conjugates of peptides and PEG linked via a -NH-C(O) spacer (cf. col. 7; examples).
D1 is prejudicial to the novelty of the subject matter of claims 1, 5, 7, 9, 10, 16, 20, 22, 24, 25, 33 and 35.

D2 discloses conjugates of proteins and PEG comprising a cleavable spacer, such as for instance the dipeptide, Met-β-Ala (cf. examples 15 and 16; claims).
D2 is prejudicial to the novelty of the subject matter of claims 1, 2, 5, 7, 9, 10, 16, 17, 20, 22, 24, 25, 31-33 and 35.

D3 discloses conjugates of proteins and PEG comprising the spacer β-Ala (cf. examples; claims).
D3 is prejudicial to the novelty of the subject matter of claims 1, 2, 5, 7, 9, 10, 16, 17, 20, 22, 24, 25, 31-33 and 35.

D4 discloses peptides having thrombopoietin activity (cf. claims). D4 anticipates to modify these peptides by PEGylation (cf. p. 41, Fig's 2 and 3). The PEGylated peptides of Fig 2 and 3 are prejudicial to the novelty of the subject matter of claim 1, because of the open ended interpretation of the term "spacer". The examiner considers the -NH-C(O)- bond in the -Gly-Lys-Gly- can be seen as the spacer.
Therefore, D4 is considered to prejudice the novelty of the subject matter of claims 1, 5, 7, 9, 11-13, 15, 16, 20, 22, 24, 26-28, 30, 33 and 35.

D5 discloses peptides that bind to the thrombopoietin receptor. The peptides are provided as dimers linked by a Lys, and are PEGylated (cf. p. 10, 13; scheme 1; claims).
The conjugate di-PEG(20K) AF15705 on p. 13, l. 15 is prejudicial to the novelty of claims 1, 5, 7, 9, 11-13, 15, 16, 20, 22, 24, 26-28, 30, 33 and 35.

D6 relates to conjugates comprising erythropoietin receptor agonists and PEG. In example 1 mPEG was conjugated to the peptide with the AA sequence GGTYSCHFGPLTWVCKPQGG. It is stated that two types of conjugates were obtained, one with one PEG and the other with 2 PEG molecules.

These conjugates are prejudicial to the novelty of the subject matter of claims 1, 5, 7, 9, 10, 12-14, 16, 17, 20, 22, 24, 25, 27-29, 33 and 35.

D7 relates to peptides that bind to the thrombopoietin receptor (cf. claims). D7 anticipates to PEGylate these peptides (p. 41, l. 5). D7 does however not actually disclose any PEGylated ligands for the thrombopoietin receptor.

D8 discloses that a dimeric form of an erythropoietin mimetic peptide displays a 100-fold increased affinity for the erythropoietin receptor.

D9 is a review directed to conjugates comprising a PEG moiety and a drug. Although D9 is mainly directed to non-peptidic drugs, such as AraC, Dox, DNR, MP, etc. (cf. p. 234), it discloses that PEGylation of proteins is standard practice in the art. On p. 235, 236, 238, 240, and 242 several conjugates are disclosed that differ only from the subject matter of invention 2 of the present application in that the drug does not comprise peptide. In Fig 15 (p. 240) however a conjugate is disclosed comprising a PEG moiety, a spacer ~/NH(-CH2-O)2-CH2-C(O)-, a peptide moiety comprising linker, and the drug AraC. It follows that this compound is prejudicial to the novelty of claims 1-3, 5, 10, 12, 16-18, 20, 25, 27, 33, 35. The attention of the applicant is further directed to the conclusion section of D9.

D10 relates to the release of proteins from the conjugated PEG moiety. It discloses in scheme 1 conjugate 13a which comprises a peptide (eg. lysozyme, IL-2, GFP), a releasable linker, a spacer (eg. β-alanine) and one or more 12 kD mPEG moieties. D10 is prejudicial to the novelty of the subject matter of claims 1, 2, 5, 7, 9, 10, 16, 17, 20, 22, 24, 25, 31-33, 35.

D11 discloses conjugates comprising a hydroxy or amine comprising drug (eg. protein enzyme, etc. (cf. [0060-0067], a linker, a spacer and a hydrophilic polymer (eg. PEG). The invention is exemplified with non-peptidic drugs (see eg. Fig. 8, compounds 32B,C,F; 37B,C,F; 44B,C,F; 48B,C,F; 56,64).

D12 provides peptides that bind to and activate the thrombopoietin receptor. The provision of dimers of such peptides results in an increase of the activity (cf. table 9 and 10). Interestingly D13 discloses that such dimerized peptides can be PEGylated (cf. Fig's 5 and

6)

D14 discloses conjugates of a biologically active material (eg. with a water-soluble non-antigenic polymer (eg. PEG). The attention of the applicant is directed to the antigenic polymer disclosed in example 17.

D15 describes conjugates comprising a polymer (eg. PEG), a multivalent linker, and multiple prodrugs linked to the linker via a spacer comprising the structure -N-(CH2-CH_2-O)$_2$-L2- (see for instance claim 18).

To summarize: the subject matter of claims 1-3, 5, 7, 9-18, 20, 22, 24-33 and 35 lack novelty over the cited prior art documents (Art. 33(2) PCT).

Claims 4, 6, 8, 19, 21, 23, 34 and 36 appear to contain features which alone or in combination with the claims to which they refer do not appear to have been disclosed in the cited prior art. The subject matter of said claims therefore appears to be novel (Art. 33(2) PCT).

Inventive step (Art. 33(3) PCT).

An inventive step objection can either be formulated starting from the prior art disclosing the preferred peptides of the conjugate (eg. D5, D6, D12, D13) or from the prior art disclosing the preferred spacers of the present application (eg. D2, D3, D9, D11, D14, D15).

In the first instance the problem to be solved can be seen as the provision of a further spacer for the peptide-PEG conjugate. In the second instance the problem to be solved can be seen as the provision of a further peptide to be PEGylated using a β-Ala spacer.

In both instances the solution of the applicant as defined in inventions 1 and 2 appears obvious in view of a combination of the documents D2/D3/D9/D11/D14/D15 with D5/D6/D12/D13.

The remaining novel feature, the Mw of the PEG moiety, appears to be feature that needs to be selected based on the desired application (optimization of the bioavailability by

optimizing the length of the PEG moiety), and therefore lacks an inventive step (cf.§6 of D9).

To summarize: the subject matter of the present application lacks an inventive step.

Industrial applicability (Art. 33(4) PCT).

The subject matter of claims 1-36 meets the requirement of industrial applicability.